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METHOD OF TREATING MOVEMENT DISORDERS USING BARBITURIC ACID DERIVATIVES

This application claims the benefit of prior U.S. Provisional Application No. 60/432,470, filed December 11, 2002, the entire contents of which are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to the treatment of movement disorders, such as essential tremor, through the administration of one or more of 5,5 diphenyl barbituric acid and derivatives thereof.

BACKGROUND OF THE INVENTION

Movement Disorders

Movement disorders include a wide variety of disease states and physiological conditions. Non-limiting examples include various dyskinesias such as tremor, dystonia, chorea, athetosis, tic disorders, blepharospasm, as well as hemiballismus, myoclonus, focal dystonias, such as writer's cramp and torticollis, restless leg syndrome and asterixis. These excessive or otherwise abnormal involuntary movements may vary significantly in rate, frequency, periodicity and progressionary character. Such movements may be seen in sometimes overlapping disorders such as Parkinson's disease; essential tremor, a.k.a. benign tremor or familial tremor; tic disorders, e.g. Tourette's syndrome; idiopathic

dystonia (inducing writer's cramp), progressive supranuclear palsy and Wilson's disease. Movement disorders are different from seizure disorders in that movement disorders are often suppressible, they often subside or are absent during sleep and are distractable and not associated with the loss of consciousness.

5 Tremor is the most common of all movement disorders. Tremor is defined as an involuntary rhythmic, oscillatory movement about a joint produced by contractions of reciprocally innervated agonist/antagonist muscles, and is repetitive and regular in frequency. (Essential Tremor: A Practical Guide to Evaluation, Diagnosis, and Treatment, *Clinician*, Vol. 19 (No. 2), pgs. 1-15, 2001). It also ranks as one of the most
10 debilitating symptoms in all of neurology. For example, the presence of even mild tremor in the upper extremities can make even the simplest of tasks impossible to perform. (Wasielewski P.G. et al., Pharmacologic Treatment of Tremor, *Movement Disorders*, Vol. 13, Supplement 3, 1998, pp 90-100). Essential tremor and tremor associated with Parkinson's disease are the most common types of tremor encountered in
15 clinical practice. (Wasielewski P.G. et al., Pharmacologic Treatment of Tremor, *Movement Disorders*, Vol. 13, Supplement 3, 1998, pp 90-100).

Essential tremor is the most common form of tremor and of all movement disorders and perhaps the most common primary neurological disorder. Estimates of the prevalence in the elderly population range from 1 to 22%, with 1-2% being a
20 conservative number. (Findley L.J., Epidemiology and Genetics of Essential Tremor, *Neurology*, 2000, 54 (Suppl. 4), S8-S13). While often a minor problem and unassociated with other disease (hence the term "benign tremor or benign essential tremor"), it causes significant motor impairment for many individuals. In its classic form, it is a tremor involving the upper extremities and/or the head. Usually, it has a frequency of 5-8 Hz, is
25 absent with rest, presents with a sustained posture and is not significantly exacerbated by movement. (Marsden CD. Origins of Normal and Pathological Tremor in Movement Disorders : *Tremor*. Eds. L.J. Findley and R. Capildeo, New York. Oxford University Press, 1984, pp. 37-84).

The cause and pathophysiology of essential tremor remain unknown. No
30 pathologic substrate has been demonstrated in autopsy studies. Positron emission tomography (PET) studies of glucose metabolism and blood flow have demonstrated only

general findings of increased activity in the brain stem (medulla), thalamus, cerebellum, striatum and sensorimotor cortex.

Parkinson's disease is a progressive disorder with a prevalence of 1-2% in people over the age of 50. It has a worldwide distribution and has no gender preference. Unlike essential tremor, untreated Parkinson's disease is life shortening. Symptoms of the disease include (1) shaking of the hands, arms, legs or feet while the patient is resting (the shaking may be more noticeable on one side of the body, and it may affect the hands more than the feet, the shaking often stops, however, as soon as the patient moves his limbs); (2) slowness of movement or a brief, temporary delay in movement; (3) difficulty in maintaining one's balance; (4) rigidity or stiffness of the patient's limbs; (5) facial masking (a still facial expression with fewer blinks of the eyes); (6) difficulty in speech; (7) difficulty swallowing; and (8) chorea and dystonic posturing, particularly as a side effect of treatment with dopaminergic agents. As the Parkinson's disease progresses, patients may be forced to work fewer hours and cut back on their activity level. Simple tasks become more of a challenge, and they may need some help from family and friends. Patients may find that using a wheelchair helps them move around more easily, and they may need help with daily activities.

Current Treatment of Movement Disorders

1. Treatment of Essential Tremor

Alcohol remains the most effective single agent for treatment of essential tremor. Estimates of patients responsive to alcohol range from 50-90%. (Koller, W.C., Hristove, A., Brin, M. Pharmacologic Treatment of Essential Tremor. Neurology 2000; 54 (Suppl 4), pp. S30-S38.) Its effect may be dramatic in some individuals. However, the half-life of alcohol is brief and the side effects are numerous.

Beta-adrenergic receptor blocking agents such as propranolol have also been widely used for over 30 years. However, even when beneficial, the clinical response is variable and incomplete. Moreover, beta-adrenergic blockers are probably of no benefit in 50% or more of patients.

The anticonvulsant primidone has been demonstrated to be effective in a significant subpopulation of patients. Comparative studies of primidone and beta-blocking agents variously report either therapeutic equivalency or slightly greater

efficacy for primidone. Primidone, unlike beta-blocking drugs, will completely suppress tremor in some patients. (Findley, L.J., Cleaves, L., Caletti, S. Primidone in Essential Tremor of the Hands and Head : A Double Blind Controlled Clinical Study. *J. Neurol Neurosurg Psych*, 1985, 48, pp. 911-915.) Primidone, however, produces a high incidence of side effects. Furthermore, primidone has little or no effect on head tremor, even in patients with a positive response of the limbs. Primidone is converted into two active metabolites, phenobarbital and phenylethylmalonamide (PEMA). PEMA has been found to have no anti-tremor effect.

Phenobarbital has some anti-tremor effect, but not as prominent as primidone or beta-blocking agents, particularly when the patients are assessed in terms of functional improvement. (Findley, L.J. The Pharmacology of Essential Tremor in *Movement Disorders* 2nd Edition. Morsden, C.D., Fahn S, Longdong : Butterworths, 1987. As detailed below, phenobarbital has sedative effects and can suppress respiration.

There have been brief reports of newer anticonvulsant drugs, particularly gabapentin, providing a benefit in treatment of essential tremor. (See Gironell, A., Kulisevsky, J., Lopez-Villegas, D., Hernandez, G., Pascual-Sedano, B., A Randomized Placebo-Controlled Comparative Trial of Gabapentin and Propranolol in Essential Tremor. *Arch. Neurol.*, 1999, 56, pp. 475-480.) None of these other agents, however, have gained wide use for this indication, presumably because of their neurological side effects and/or limited efficacy. Methazolamide, a carbonic anhydrase inhibitor, has been reported to be of some benefit. (Meunter, M.D., Daube, J.R., Caviness, J.N., Miller, P.M. Treatment of Essential Tremor with Methazolamide. *Mayo Clinic Proc*, 1991, 66, pp. 991-997.) However, primidone and propranolol are the only two prescription drugs with proven efficacy in general clinical practice. Louis, E.D., *N. Eng. J. Med.*, 345, (12), 2001, pp. 887-891.

United States Patent No. 6,281,207 to Richter *et al.* discloses methods of combating movement disorders such as tremor by administering mirtazapine.

Surgical treatment of severe disabling essential tremor is sometimes useful. This has most commonly involved thalamotomy (lesioning of the thalamus) and, more recently, the use of surgically implanted electrodes. These procedures however have considerable potential morbidity.

2. Treatment of Parkinson's Disease

The side effects of levodopa include nausea, vomiting, loss of appetite, rapid heart rate, and lowered blood pressure when a person stands from a sitting position. To reduce these side effects, levodopa is often prescribed in combination with carbidopa, and this drug combination is marketed under the trademark Sinemet™ (Bristol-Myers Squibb). The carbidopa in Sinemet™ prevents levodopa from being metabolized in the stomach and liver, so more of the levodopa can get to the brain, which permits administration of a smaller dose of levodopa or alternatively increases the effectiveness of a given administered dose of levodopa. Even though carbidopa helps to reduce the side effects of levodopa, many patients who take Sinemet™ may still experience nausea, vomiting, and loss of appetite when they begin taking it or after their dosage is increased. Other side effects of carbidopa/levodopa combination medications include dry mouth, daytime sleepiness, nervousness, vivid dreams, insomnia, and a form of motor fluctuation called

dyskinesia, characterized by involuntary writhing movements. Sometimes dyskinesia results when the dosage of the medication is too high.

Another group of medications for Parkinson's Disease is dopamine agonists.

Dopamine agonists are drugs that stimulate the parts of the human brain that normally

5 respond to dopamine. In effect, the brain "thinks" it is receiving dopamine, so these drugs help satisfy the brain's need for dopamine. The most commonly used dopamine

agonists in the United States include Parlodel™ (bromocriptine, Novartis), Permax™ (pergolide mesylate, Amarin), MIRAPEX™ (pramipexole hydrochloride, Pharmacia & Upjohn) and Requip™ (ropinirole, GlaxoSmithKline). Parlodel™ and Permax™ are

10 synthetic derivatives of a chemical called "ergot". The side effects are similar to those of levodopa: nausea, vomiting, confusion, hallucinations, lightheadedness and fainting. A

rare side effect known as fibrosis (membrane lining of body organs can become

thickened or scarred) has also been reported. MIRAPEX™ has been shown to be

effective in treating the symptoms of early disease without levodopa. During the

15 advanced stages, taking MIRAPEX™ in combination with levodopa may reduce the dose of levodopa that is needed. The use of MIRAPEX™ can cause drowsiness and the

possibility of suddenly falling asleep during daily activities, which could result in an

accident while driving. The most common side effects of MIRAPEX™ are nausea, sleeplessness, constipation, involuntary movement, sleepiness, dizziness upon standing,

20 and hallucinations.

Another group of medications for Parkinson's Disease is catechol-O-

methyltransferase (COMT) inhibitors (e.g., Tasmar™ (tolcapone, Roche Laboratories)

and Comtan™ (entacapone, Novartis)). COMT is one of two enzymes that break down

levodopa before the brain converts it into dopamine. When the COMT enzyme is blocked

25 by the COMT inhibitors, dopamine stays in the brain for a longer period of time. COMT

inhibitors are usually taken with levodopa. The most common side effects reported by

patients who have taken COMT inhibitors include unusually vivid dreams or visual

hallucinations, nausea, difficulty in sleeping, daytime drowsiness, headache, and

excessive involuntary movements. In addition, in 1998 the U.S. Food and Drug

30 Administration reported that Tasmar™ can cause liver damage, so now doctors are

advised to monitor their patients who are taking this drug on a regular basis to make sure their liver is functioning normally.

Anticholinergics have also been used in the treatment of Parkinson's disease. Before doctors begin treating Parkinson's disease patients with levodopa, they may prescribe anticholinergic drugs such as Artane™ to relieve symptoms. When the brain cannot get enough dopamine, it produces increased quantities of a chemical called acetylcholine, and too much acetylcholine causes tremor and rigidity in patients. Anticholinergic drugs block the effect of acetylcholine, so they are effective in reducing tremor and rigidity in patients. Anticholinergics are not usually prescribed for long periods of time because of the side effects they cause in patients, which include dry mouth, blurred vision, constipation, difficulty in urinating, confusion, and hallucinations.

Dopamine is broken down in the brain by an enzyme called monoamine oxidase (MAO). Hence, selegiline and other MAO inhibitors help the brain make the most of the dopamine that is still being produced and/or dopamine that is being supplied to the brain by other drugs. When a Parkinson's disease patient takes an MAO inhibitor, it slows down the progress of this enzyme, which increases the amount of dopamine that is available to the brain. The side effects of selegiline include heartburn, loss of appetite, nausea, dry mouth, dizziness, constipation, and insomnia.

Anti-viral agents such as Symmetrel™ (amantadine, Endo Labs) provide mild relief of Parkinson's symptoms in newly-diagnosed patients. It has been used to treat this disease for many years, but even today, medical researchers and doctors aren't really sure how it works in the human brain. Unfortunately, it tends to cause insomnia and daytime fatigue, and other side effects that have been reported include red or purple skin blotches (often on the patient's legs), swelling of the feet, anxiety, dizziness, difficulty in urinating, and hallucinations. (Lang, A.E. *et al.*, *N. Eng. J. Med.*, 339 (16), 1998, pp. 1130-1143).

United States Patent No. 6,281,207 to Richter *et al.* discloses methods of combating movement disorder such as Parkinson's disease by administering mirtazapine.

Surgery can dramatically reduce symptoms for some patients in the advanced stages of Parkinson's disease. Doctors may suggest surgery as an option for such patients because they have been taking combinations of drugs over a long period of time, and those drugs have become less and less effective. A pallidectomy or pallidotomy is a surgical procedure in which a lesion is created in a specific area of the brain (globus pallidus) to help restore the balance required for normal motion. The majority of patients

who have had this surgery have gained immediate, significant improvements in their ability to function, and those benefits have lasted for at least a year. Deep brain stimulation (DBS) has also been used by physicians as a preferred alternative to a pallidotomy. Although these surgical approaches have produced some desirable results, the long-term effects of such surgeries for Parkinson's patients are not yet known. Therefore, doctors generally reserve these as last resort treatments for their patients. (Lang, A.E. *et al.*, *N. Eng. J. Med.*, 339 (16), 1998, pp. 1130-1143).

In view of the above, there exists a need for a method of treating movement disorders that are either symptoms of or associated with Parkinson's disease or not using an active agent having minimal adverse side effects, high tolerance, and significant effectiveness.

Barbituric Acid Derivatives

1. Sedating Barbituric Acid Derivatives

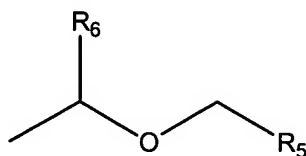
Barbiturates (or barbituric acid derivatives) have been developed and have been used as the primary drugs for the treatment of insomnia for many years. Barbiturates depress both the respiratory drive and the mechanisms responsible for the rhythmic character of respiration. (Goodman & Gilman's, *The Pharmacological Basis of Therapeutics*, Chapter 17, 9th Edition, McGraw-Hill). They have been implicated in thousands of deaths due to accidental (or deliberate) ingestion (resulting in homicide, suicide or accidental death) since they are associated with serious, often fatal, central nervous system (CNS) depressive effects following acute overdosage. Barbiturates have been chronically abused by a substantial portion of the population. When coadministered with other drugs, barbiturates may interact with them with a potentially lethal outcome. Currently or previously clinically employed barbiturates include amobarbital, barbital, butabarbital, and hexobarbital, mephobarbital, pentobarbital, phenobarbital, secobarbital, thiamylal, and thiopental. Barbiturates with a short to intermediate duration of action (e.g., amobarbital, butabarbital, pentobarbital, secobarbital, and vibarbital) are used as sedative-hypnotics. Phenobarbital is used as an anticonvulsant for the treatment of seizure disorders. Ultrashort-acting barbiturates (e.g., thiamylal and thiopental) can be used as anesthetics. (Craig, C.R. and Stitzel R.E., *Modern Pharmacology*, Chapter IV, 2nd Edition, 1986, Little, Brown and Company, Boston/Toronto).

2. Non-Sedating Barbituric Acid Derivatives

United States Patent No. 6,093,820 ("the '820 Patent") to Gutman *et al.* discloses that alkoxyalkylated ureide compounds such as N-methoxymethyl ethosuximide, N-methoxymethyl glutethimide, and N-methoxymethyl-5,5-diphenylbarbituric acid are also useful in treating convulsions, seizures, muscle stiffness, or anxiety. Again, the '820

SUMMARY OF THE INVENTION

wherein R₃ and R₄ are each independently selected from the group consisting of lower alkyl, phenyl and lower alkyl substituted phenyl, and R₁ and R₂ are each independently either a hydrogen atom or a radical of the formula



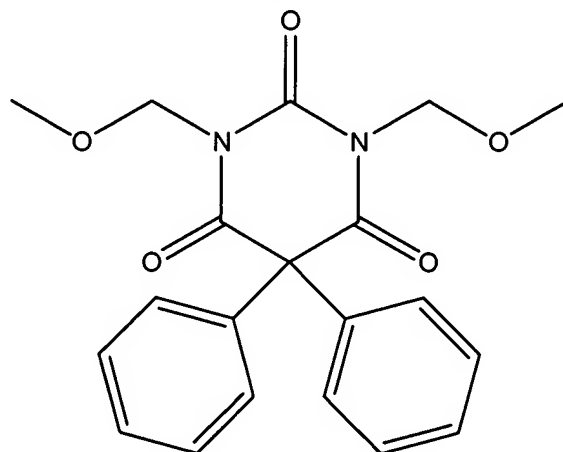
In one embodiment, the movement disorder treated with one or more of the foregoing compounds is essential tremor.

In yet another embodiment, the movement disorder is not associated with Parkinson's disease.

In a further embodiment, the movement disorder is a focal dysytonia, such as writer's cramp.

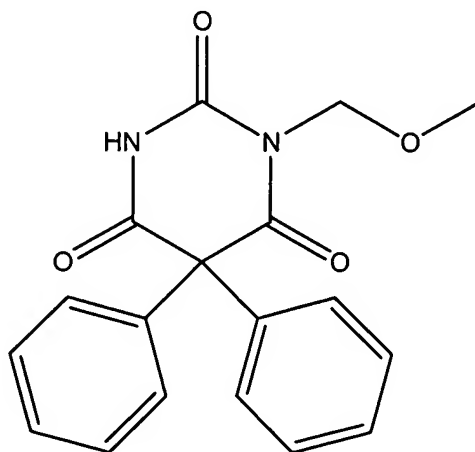
In yet a further embodiment, the movement disorder is restless leg syndrome.

According to a preferred embodiment of the present invention, a method of
5 treating essential tremor comprises administering an amount effective for that purpose of
at least one compound according to the following formula (II):



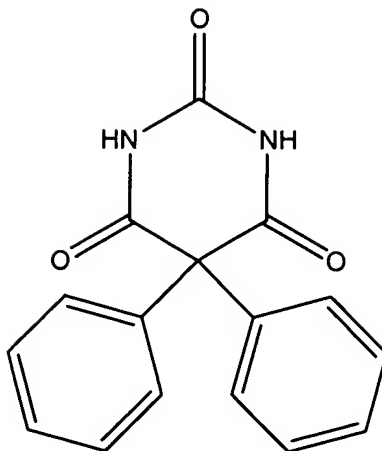
or a pharmaceutically acceptable salt, prodrug or metabolite thereof.

According to another preferred embodiment of the present invention, a method of
10 treating essential tremor comprises administering an amount effective for that purpose of
at least one compound according to the following formula (III):



or a pharmaceutically acceptable salt, prodrug or metabolite thereof.

According to a further preferred embodiment of the present invention, a method
15 of treating essential tremor comprises administering an amount effective for that purpose
of at least one compound according to the following formula (IV):



or a pharmaceutically acceptable salt, prodrug or metabolite thereof.

5

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows the mean absolute change in baseline tremor score and plasma concentrations of DMMDPB, MMMDPB, and DPB after multiple oral doses of placebo or DMMDPB in patients with essential tremor, observed during the study set forth in Example 2.

10

Figure 2 shows the mean absolute change in baseline tremor score vs. plasma concentrations of MMDPB and DPB after multiple oral doses of DMMDPB in patients with essential tremor, observed during the study set forth in Example 2.

DETAILED DESCRIPTION OF THE INVENTION

15

In describing particular embodiments of the present invention, specific terminology is employed for the sake of clarity. However, the invention is not intended to be limited to the specific terminology so selected, and it is to be understood that each specific element includes all technical equivalents which operate in a similar manner to accomplish a similar purpose. Nevertheless, certain terms are given special definitions, as follows:

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The term "combination" applied to active ingredients is used herein to define a single pharmaceutical composition (formulation) comprising at least two active ingredients or two or more separate pharmaceutical compositions (formulations), each

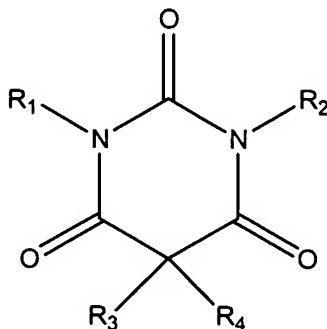
comprising at least one active ingredient, said separate formulations to be administered conjointly.

The term "conjoint administration" and its variants (e.g., "administered conjointly") is used to refer to administration of two or more active ingredients simultaneously in one composition, or simultaneously in different compositions, or sequentially. For the sequential administration to be considered "conjoint," however, the active ingredients should be administered separated by no more than a time interval that still permits the resultant beneficial effect for treating, preventing, arresting, delaying the onset of and/or reducing the risk of developing a movement disorder. For example, the active ingredients should be administered on the same day (e.g., each - once or twice daily), preferably within an hour of each other, and most preferably simultaneously.

The term "treat" and its variants (e.g., "treatment", "treating") is used herein to mean to relieve, alleviate or eliminate at least one symptom of a disease in a subject. For example, in relation to tremor, the term "treat" means to reduce or to eliminate tremor or to decrease its intensity or to improve impairment of coordination associated with tremor. Such reduction or decrease should be measurable or perceptible to the physician attending the patient.

The present invention aims to provide a method for treating movement disorders such as essential tremor or Parkinson's disease. More specifically, it aims to treat movement disorders effectively and without the severe risks and/or side effects often associated with other treatment modalities, or with a significantly reduced number of such side effects and/or risks. Such risks and side effects include but are not limited to sedation, danger of overdose, and respiratory arrest.

Cyclic ureides having the following general formula (I):



CC(R6)OCCR5

One preferred type of cyclic ureides useful in the method of the present invention are barbituric acid derivatives disubstituted at the 5-position. Another preferred embodiment of the present invention uses 5,5-diphenyl barbituric acid and derivatives for the treatment of movement disorders. Specific preferred compounds useful in the treatment method of the present invention include N,N-dimethoxymethyl diphenyl barbituric acid (DMMDPB), monomethoxymethyl diphenyl barbituric acid (MMMDPB) and diphenyl barbituric acid (DPB), and pharmaceutically acceptable salts and prodrugs thereof.

Compounds useful in the treatment method of the present invention may be formulated into compositions or formulations that additionally and optionally comprise any suitable adjuvants, excipients, additives, carriers, solvents, additional therapeutic agents (e.g., for conjoint use as a combination treatment, including for example one or more additional agents for combating the movement disorder and/or a concurrent physiological condition), bioavailability enhancers, side-effect suppressing constituents,

or other ingredients that do not adversely affect the efficacy of the composition for combating movement disorders.

Pharmaceutically acceptable salts of the movement disorder-combating compounds of the invention and physiologically functional derivatives thereof include salts derived from an appropriate base, such as an alkali metal (for example, sodium, potassium), an alkaline earth metal (for example, calcium, magnesium), ammonium and NX_4^+ (wherein X is C_1 - C_4 alkyl). Pharmaceutically acceptable salts of an amino group include salts of organic carboxylic acids, such as tartaric, aliphatic, cycloaliphatic, aromatic, heterocyclic, carboxylic and sulfonic classes of organic acids, such as, for example, formic, glucuronic, malic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, stearic, algenic, hydroxybutyric, cyclohexylaminosulfonic, galactaric and galacturonic acid and the like, lactobionic, fumaric, and succinic acids; organic sulfonic acids, such as methaniesulfonic, ethanesulfonic, isothionic, benzenylesulfonic and p-toluenesulfonic acids; and inorganic acids such as hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric, sulfamic and phosphoric acid and the like. Pharmaceutically acceptable salts of a compound having a hydroxy group consist of the anion of said compound in combination with a suitable cation such as Na^+ , NH_4^+ or NX_4^+ (wherein X is, for example, a C_1 - C_4 alkyl group), Ca^{++} , Li^+ , Mg^{++} , or, K^+ and zinc or organic salts made from primary, secondary and tertiary amines, cyclic amines, N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine and the like. All of these salts may be prepared by conventional means from the corresponding compound by reacting, for example, the appropriate acid or base with the compound in free form.

For use in treatments describes herein, salts of movement disorder-combating compounds of the invention will be pharmaceutically acceptable, i.e., they will be salts derived from a pharmaceutically acceptable acid or base. However, salts of acids or bases which are not pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether or not derived from a pharmaceutically acceptable acid or base, are within the

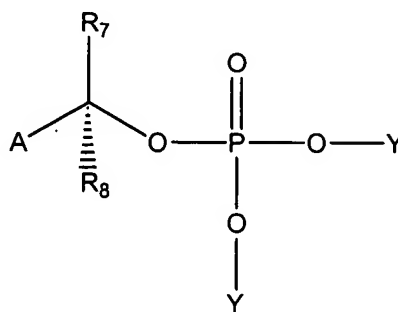
scope of the present invention. Prodrugs and active metabolites of compounds disclosed herein are also within the scope of the invention.

Prodrugs

5 A prodrug is a pharmacologically active or more typically an inactive compound that is converted into a pharmacologically active agent by a metabolic transformation. In vivo, a prodrug readily undergoes chemical changes under physiological conditions (e.g., are acted on by naturally occurring enzyme(s)) resulting in liberation of the pharmacologically active agent. Prodrugs may be administered in the same manner as
10 the active ingredient to which they convert or they may be delivered in a reservoir form, e.g., a transdermal patch or other reservoir which is adapted to permit (by provision of an enzyme or other appropriate reagent) conversion of a prodrug to the active ingredient slowly over time, and delivery of the active ingredient to the patient.

Suitable prodrugs of MMDPB include, but are not limited to, mono- and di-
15 phosphate and mono and di-phosphonooxyalkyl derivatives of MMDPB. Preferred prodrugs are the mono- and di-phosphonooxymethyl derivatives.

An exemplary method for synthesis of the prodrugs involves a derivatizing agent represented by the formula shown below:



20 wherein A is any leaving group that is displaced by a nucleophilic tertiary amine group in the compounds of the present invention. Suitable examples of the leaving group A include, but are not limited to, tosylate, triflate, iodine, bromine, chlorine, acetate and hydroxyl. Further discussion of suitable leaving groups may be found in Hatshorn, S.R., Aliphatic Nucleophilic Substitution, Cambridge University Press, 1973.

25 R_7 and R_8 independently represent any suitable organic or inorganic residue, such as, but not limited to, straight chain or branched alkyl, such as methyl, ethyl, propyl, etc.,

Each Y independently represents a phosphate protecting group, such as, but not limited to, methyl, ethyl, tertiary butyl, benzyl, isopropyl, or more generally lower (C₁ - C₄) alkyl or benzyl. Other suitable examples of phosphate protecting groups may be found in Green T.W., *et al.*, Protective Groups In Organic Synthesis, 2nd Ed., Wiley, New York, 1991.

Reaction scheme showing the synthesis of a 1,3-dihydro-2H-imidazo[4,5-b]pyridine derivative:

Starting materials:

- 1,3-dihydro-2H-imidazo[4,5-b]pyridine derivative (with substituents R_1, R_2, R_3, R_4)
- Phosphonate ester (with substituents R_7, R_8 and groups A, Y)

Reaction conditions:

- Proton Scavenger

Intermediate:

- 1,3-dihydro-2H-imidazo[4,5-b]pyridine derivative (with substituents R_1, R_2, R_3, R_4)
- Phosphonate ester (with substituents R_7, R_8 and groups A, Y)
- Counterion: A^-

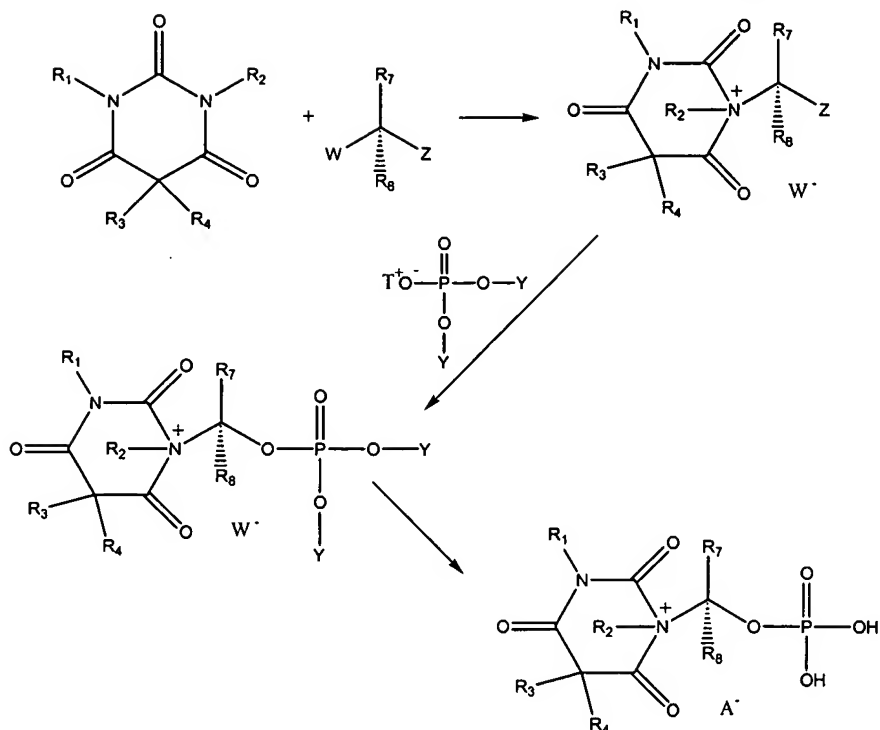
Final step:

- Trifluoroacetic Acid

Final product:

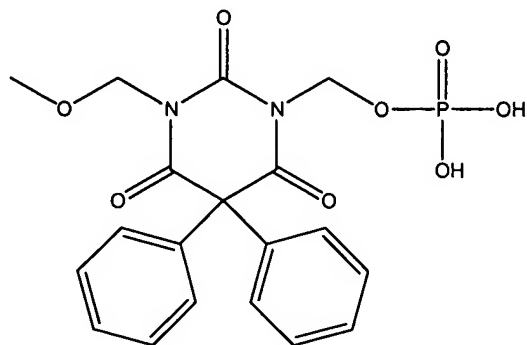
- 1,3-dihydro-2H-imidazo[4,5-b]pyridine derivative (with substituents R_1, R_2, R_3, R_4)
- Phosphonate ester (with substituents R_7, R_8 and groups A, Y)
- Counterion: A^-

An alternate synthesis of the prodrugs is shown in the scheme below.



wherein W and Z are leaving groups similar to A, and can be the same or different. T is any organic or inorganic cationic species. Suitable reaction conditions for synthesis of the prodrugs are set forth in U.S. Patent No. 5,985,856, which is hereby
 5 incorporated by reference in its entirety. The following are non-limiting examples of prodrugs specifically contemplated for use in the present invention:

Formula (V)



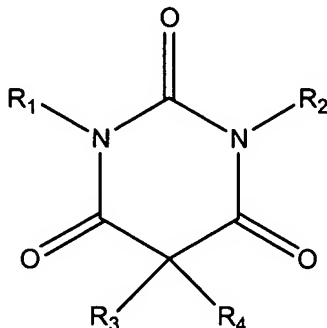
O=P([O-])([O-])OCCN1C(=O)N(COP(=O)([O-])[O-])C(=O)C2(c3ccccc3C(=O)N1C2=O)c4ccccc4O=P(O)(O)OCCN1C(=O)C(=O)C2(C1)C(=O)C(=O)C2c3ccccc3

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The present invention also contemplates the treatment of movement disorders using pharmaceutical dosage forms containing at least one compound of the following formula:



5 or a pharmaceutically acceptable salt, metabolite, or prodrug thereof, wherein R₁, R₂, R₃ and R₄ are as described, *supra*, both for veterinary and for human medical use.

In such pharmaceutical dosage forms, the active agent preferably is utilized together with one or more pharmaceutically acceptable carrier(s) therefore and optionally any other therapeutic ingredients. The carrier(s) must be pharmaceutically acceptable in
10 the sense of being compatible with the other ingredients of the formulation and not unduly deleterious to the recipient thereof.

A subject in whom administration of the therapeutic compound is an effective therapeutic regimen for a disease or disorder is preferably a mammal, more preferably a human, but can be any animal, including a laboratory animal in the context of a clinical
15 trial or screening or activity experiment employing an animal model. Thus, as can be readily appreciated by one of ordinary skill in the art, the methods and compositions of the present invention are particularly suited to administration to any animal, particularly a mammal, and including, but by no means limited to, domestic animals, such as feline or canine subjects, farm animals, such as but not limited to bovine, equine, caprine, ovine,
20 and porcine subjects, research animals, such as mice, rats, rabbits, goats, sheep, pigs, dogs, cats, etc., avian species, such as chickens, turkeys, songbirds, etc., i.e., for veterinary medical use.

Depending on the specific movement disorder to be treated, a suitable therapeutically effective and safe dosage, as may readily be determined within the skill of
25 the art, and without undue experimentation, maybe administered to subjects.

Effective Amounts

In general, while the effective dosage of compounds of the invention for therapeutic use in accordance with the inventions may be widely varied, depending on the specific application, movement disorder, or physiological state involved, as readily
5 determinable within the skill of the art, suitable effective doses of the compounds and compositions described herein, and for achievement of a benefit in treatment, will broadly be in the range of 10 micrograms (μg) to 150 milligrams (mg) per kilogram body weight of the subject per day, preferably in the range of 50 μg to 130 mg per kilogram body weight per day, and most preferably in the range of 100 μg to 120 mg per kilogram
10 body weight per day. The desired dose may be presented as one or more sub-dose(s) administered at appropriate intervals throughout the day, or alternatively in a single dose, preferably for morning or evening administration. These daily doses or sub-doses may be administered in unit dosage forms, for example, containing from about 150 mg to about 1500 mg, preferably from about 200 mg to about 1200 mg, more preferably from about
15 250 mg to about 850 mg, and most preferably about 450 mg of active ingredient per unit dosage form to be administered daily or twice daily. In specific embodiments, the daily dosage is equal to or greater than about 200, 250, 300, 350, 400, 450 mg of active ingredient per unit dosage form to be administered daily or twice daily. Typically, less than about 1500 mg of active ingredient of active ingredient per unit dosage form or
20 preferably less than about 1200 mg is to be administered daily. Alternatively, if the condition of the recipient so requires, the doses may be administered as a continuous or pulsatile infusion. The duration of treatment may be decades, years, months, weeks, or days, as long as the benefits persist.

It is appreciated that the effective dose(s) may vary depending on the patient's
25 age, sex, physical condition, duration and severity of symptoms, duration and severity of the underlying disease or disorder if any, and responsiveness to the administered compound. Accordingly, the foregoing ranges are guidelines and subject to optimization, and because of the good tolerability and low toxicity of the compounds of the present invention, higher doses may be administered. Effectiveness of a dose can be assessed
30 using e.g., the criteria described in Fahn S. *et al.*, Clinical rating scale for tremor, In: Parkinson's Disease and Movement Disorders, Jancovic J., Tolosa E. (Eds.) 1998 Urban

& Swarzenberg, Inc. Baltimore, MD, USA 225-234, this section being incorporated by reference.

The mode of administration and dosage forms is closely related to the therapeutic amounts of the compounds or compositions which are desirable and efficacious for the given treatment application.

Suitable dosage forms include but are not limited to oral, rectal, sub-lingual, mucosal, nasal, ophthalmic, subcutaneous, intramuscular, intravenous, transdermal, spinal, intrathecal, intra-articular, intra-arterial, sub-arachinoid, bronchial, lymphatic, and intra-uterine administration, and other dosage forms for systemic delivery of active ingredients. Formulations suitable for oral administration are preferred.

To prepare such pharmaceutical dosage forms, one or more of the aforementioned compounds of formula (I) are intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration.

In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Thus, for liquid oral preparations, such as, for example, suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like. For solid oral preparations such as, for example, powders, capsules and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Due to their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form. If desired, tablets may be sugar coated or enteric coated by standard techniques.

For parenteral formulations, the carrier will usually comprise sterile water, though other ingredients, for example, ingredients that aid solubility or for preservation, may be included. Injectable solutions may also be prepared in which case appropriate stabilizing agents may be employed.

In some applications, it may be advantageous to utilize the active agent in a "vectorized" form, such as by encapsulation of the active agent in a liposome or other encapsulant medium, or by fixation of the active agent, e.g., by covalent bonding, chelation, or associative coordination, on a suitable biomolecule, such as those selected from proteins, lipoproteins, glycoproteins, and polysaccharides.

Treatment methods of the present invention using formulations suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets, or lozenges, each containing a predetermined amount of the active ingredient as a powder or granules. Optionally, a suspension in an aqueous liquor or a non-aqueous liquid may be employed, such as a syrup, an elixir, an emulsion, or a draught.

A tablet may be made by compression or molding, or wet granulation, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, with the active compound being in a free-flowing form such as a powder or granules which optionally is mixed with a binder, disintegrant, lubricant, inert diluent, surface active agent, or discharging agent. Molded tablets comprised of a mixture of the powdered active compound with a suitable carrier may be made by molding in a suitable machine.

A syrup may be made by adding the active compound to a concentrated aqueous solution of a sugar, for example sucrose, to which may also be added any accessory ingredient(s). Such accessory ingredient(s) may include flavorings, suitable preservative, agents to retard crystallization of the sugar, and agents to increase the solubility of any other ingredient, such as a polyhydroxy alcohol, for example glycerol or sorbitol.

Formulations suitable for parenteral administration usually comprise a sterile aqueous preparation of the active compound, which preferably is isotonic with the blood of the recipient (e.g., physiological saline solution). Such formulations may include suspending agents and thickening agents and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. The formulations may be presented in unit-dose or multi-dose form.

Parenteral administration may comprise any suitable form of systemic delivery or delivery directly to the CNS. Administration may for example be intravenous, intra-arterial, intrathecal, intramuscular, subcutaneous, intramuscular, intra-abdominal (e.g., intraperitoneal), etc., and may be effected by infusion pumps (external or implantable) or any other suitable means appropriate to the desired administration modality.

Nasal and other mucosal spray formulations (e.g. inhalable forms) can comprise purified aqueous solutions of the active compounds with preservative agents and isotonic agents. Such formulations are preferably adjusted to a pH and isotonic state compatible with the nasal or other mucous membranes. Alternatively, they can be in the form of

finely divided solid powders suspended in a gas carrier. Such formulations may be delivered by any suitable means or method, e.g., by nebulizer, atomizer, metered dose inhaler, or the like.

Formulations for rectal administration may be presented as a suppository with a suitable carrier such as cocoa butter, hydrogenated fats, or hydrogenated fatty carboxylic acids.

Transdermal formulations may be prepared by incorporating the active agent in a thixotropic or gelatinous carrier such as a cellulosic medium, e.g., methyl cellulose or hydroxyethyl cellulose, with the resulting formulation then being packed in a transdermal device adapted to be secured in dermal contact with the skin of a wearer.

In addition to the aforementioned ingredients, formulations of this invention may further include one or more accessory ingredient(s) selected from diluents, buffers, flavoring agents, binders, disintegrants, surface active agents, thickeners, lubricants, preservatives (including antioxidants), and the like.

The formulation of the present invention can have immediate release, sustained release, delayed-onset release or any other release profile known to one skilled in the art.

Pharmacokinetic studies of DMMDPB suggest that in humans the drug is rapidly metabolized to MMMDPB and then slowly metabolized to DPB. DBP has been shown to exert anticonvulsant properties in several animal models of seizure activity. (However, the present inventor has indications that in movement disorders MMMDPB may be active itself.) In any event, the administration of DMMDPB results in a sustained source of DPB, which has been shown to provide prolonged anticonvulsant activity.

DMMDPB, is a member of a class of nonsedating barbiturate compounds. It has been demonstrated in animal models to retain the anticonvulsant properties of phenobarbital ('056 Patent). Thus, it offers the possibility of a broad spectrum, barbiturate anticonvulsant without the dose limiting side effect of sedation. By eliminating sedation, and thus increasing the tolerable dose, DMMDPB further offers the possibility of a more effective anticonvulsant by virtue of enabling the use of higher dosages. It is anticipated that these beneficial properties persist when this compound (or its metabolite e.g., MMMDPB and DPB) is used to treat movement disorders.

DMMDPB is a pro-drug and is converted to MMMDPB which in turn is converted to DPB, an active metabolite of DMMDPB. The latter conversion has been

MMMDPB and DPB on Days 13, 14 and 15 neurological changes were observed. DMMDPB had no clear effect on cognitive or psychomotor functions with increasing dose.

A Phase I clinical study was performed in a total of 16 healthy male subjects. 12 subjects received DMMDPB and 4 subjects received placebo. 15 subjects successfully completed the study. The subjects were healthy, non-smoking males between 18 and 55 years of age. A total of 28 doses of DMMDPB were administered orally, given twice daily for two weeks. Doses were either 450 mg or 600 mg under fed conditions.

DMMDPB was well tolerated. Minor adverse events were observed that also occurred with the placebo subjects. DMMDPB, MMMDPB and DPB pharmacokinetics showed near linearity up to 600 mg. Minimum plasma concentrations of DMMDPB, MMMDPB and DPB on Days 13, 14 and 15 indicate that steady-state (DMMDPB, MMMDPB) and near steady-state (DPB) was achieved with 14 days of dosing (28 doses). No neurological changes were observed. DMMDPB had little or no effect on cognitive or psychomotor functions.

It is expected that treatment with non-sedating barbiturates may be effective for therapy in controlling all movement disorders. Specifically, stimulation of the ventral intermediate nucleus of the thalamus appears to be very effective in the treatment of tremor, not only in patients having Parkinson's disease but also in patients with essential tremor. Lozano. Arch. Med. Res. 2000, 31(3):266-269; Kiss *et al.*, Neuroscience, 2002, 113(1):137-143. Stereotactic thalamotomy has been used in selective cases to treat Parkinson's disease as well as essential tremor. Balas *et al.*, Rev. Neurol. 2001, 32(6):520-524. These findings suggest that the neurologic substrate necessary for the generation of tremor in Parkinson's disease and essential tremor may be similar, and the present inventor fully anticipates them to respond to the same treatment. Moreover, the observational evidence adduced by the present inventor that the present treatment is effective for focal dystonias, such as writer's cramp, supports the notion that the present invention is effective for the treatment of all movement disorders, whether associated with a disease such as Parkinson's or essential tremor, or one of unknown, or idiopathic origin.

EXAMPLES

The features and advantages of the invention are more fully shown by the following non-limiting examples.

5

Example 1 - Synthesis of MMMDPB

A reactor was charged with chlorobenzene (15 ml), and stirring and an N₂ flow were started. N,N'-bismethoxymethyl barbituric acid (1.84 g) was added to the reactor. The mixture was stirred for 10 minutes and then heated up to 55-60° C. The mixture was stirred for another 10 minutes. Aluminum chloride (AlCl₃, 0.66 g) was added. The mixture was stirred for 10 minutes at about 60° C. The mixture was heated up to 100-110° C and stirred for another 10 minutes. The mixture was cooled to 60° C. The N₂ flow was stopped. A cold solution of hydrochloric acid (32%, 0.5 ml) in deionized water (30 ml) was added. The mixture was stirred at 5° C for about 30 minutes. The suspension was filtered, and the filter cake was washed with cold chlorobenzene (2 ml). The filtrate from the washing was added to the filtrate from the filtration. The chlorobenzene (lower) phase was separated. The majority of chlorobenzene from the lower phase was allowed to evaporate. The resulting residue was diluted with ethyl acetate (10 ml). The solution was extracted with 0.5 N sodium hydroxide (15 ml), while maintaining the temperature of the solution at 20° C or lower. The ethyl acetate phase was washed with cold deionized water (15 ml). Water was added to the basic extract. The extract was acidified with a hydrochloric acid solution (32%, 1 ml), while maintaining its temperature below 20 °C. The mixture was stirred for 30 minutes. The suspension was then filtered. The filter cake was washed with deionized water (5 ml) to yield crude MMMDPB.

The crude product was purified as follows. A second reactor was charged with ethanol (95%, 4.5 ml). Stirring was started. The crude MMMDPB (0.87 g) was added to the reactor. The mixture was heated up to 60° C and stirred for about 30 minutes. The mixture was cooled to room temperature and stirred for about 30 minutes. The resulting suspension was filtered. The filter cake was washed with ethanol (95%, 1 ml). The wet product was dried in a vacuum oven at 60° C for about 10 hours.

Twelve patients were selected using criteria for definite essential tremor as classified by the National Institute of Health (NIH) Diagnostic Criteria for Essential Tremor and the Tremor Investigation Group (TRIG) Proposed Criteria for Diagnosing Essential Tremor. See Jankovic J. Essential Tremor: Clinical Characteristics, *Neurology*, 2000;54 (Suppl 4); S21-25, incorporated by reference in its entirety. According to these protocols, patients must have bilateral postural tremor of both upper extremities with an amplitude rating of 2 or greater in one arm and 1 or greater in the other, which is visible, persistent, and longstanding (preferably > 3 years). Patients were tapered off medications and vitamins, energy drinks, grapefruit and supplements 7 days prior to the commencement of the study. They were instructed to stop tremor medications 14 days prior to study commencement, after taper. There were some dietary restrictions:

Evaluations of tremor were conducted with at least one of a clinical rating scale, a patient-reported disability/symptom scale, and neurophysiological measurements, such as accelerometric recordings. Since the correlation between accelerometry scores and functional disability scores has been subject to criticism in the literature, clinical grading scales and patient reporting were used as the primary parameters.

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14 days. Placebo patients exhibited less than 50% improvement. The level of improvement shown in the drug-treated patients was statistically significant ($p < 0.02$) by one-tail t test.

5

TABLE 1

	Drug Response			(C - B)		(D - B)		(D - C)	
Subject#	Baseline Score "B"	Avg. of days/1,2,4 "C"	Avg. of days 6, 8, 10, 12, 14 "D"	Absolute First Period Change	First Period % Change	Overall Change @14 days	Overall % Change	Second Period Difference	Second Period % Change
9	31.0	11.3	6.8	(19.7)	-64%	(24.2)	-78%	(4.5)	-40%
3	33.0	15.7	9.5	(17.3)	-52%	(23.5)	-71%	(6.2)	-39%
7	20.0	10.7	6.2	(9.3)	-47%	(13.8)	-69%	(4.5)	-42%
4	25.0	18.3	15.2	(6.7)	-27%	(9.8)	-39%	(3.1)	-17%
6	17.0	10.7	9.8	(6.3)	-37%	(7.2)	-42%	(0.9)	-8%
11	16.0	9.7	9.2	(6.3)	-39%	(6.8)	-43%	(0.5)	-5%
8	21.0	15.0	9.2	(6.0)	-29%	(11.8)	-56%	(5.8)	-39%
2	24.0	18.7	11.8	(5.3)	-22%	(12.2)	-51%	(6.9)	-37%
10	14.0	9.0	8.0	(5.0)	-36%	(6.0)	-43%	(1.0)	-11%
1	17.0	14.0	13.8	(3.0)	-18%	(3.2)	-19%	(0.2)	-1%
12	22.0	19.0	13.8	(3.0)	-14%	(8.2)	-37%	(5.2)	-27%
5	22.0	20.7	13.8	(1.3)	-6%	(8.2)	-37%	(6.9)	-33%

The mean absolute change in baseline tremor score and plasma concentrations of DMMDBP, MMMDPB, and DPB is shown in Table 2, and Figure 1.

TABLE 2

Time		Absolute Change in Baseline Tremor Score		Plasma Concentration (µg/ml)		
Days	Hours	Placebo	Drug	DMMDPB	MMMDPB	DPB
1	0	0	0	0.00	0.00	0.00
1	1	ND	ND	0.03	0.21	0.11
1	2	ND	ND	0.19	0.71	0.29
1	4	ND	ND	0.33	1.73	0.97
1	8	ND	ND	0.11	1.27	1.44
1	12	-5	-10	0.10	1.22	1.78
2	36	-3	-12	0.42	4.96	3.72
4	84	-7	-14	0.50	11.50	9.11
6	132	-8	-16	0.37	14.54	14.67
8	180	-8	-17	0.33	17.61	21.23
10	228	-7	-18	0.27	18.27	25.62
12	276	-7	-19	0.22	17.96	30.13
14	324	-9	-18	0.19	16.21	33.90
16	372	-7	-11	0.07	9.12	32.74
18	420	-6	-5	0.03	5.43	25.70
20	468	-3	-3	0.03	1.37	14.13
22	516	-9	-3	0.02	0.31	7.68
24	684	-7	-6	ND	ND	ND

ND = Not Determined

The mean absolute change in baseline tremor score vs. plasma concentrations of MMDPB and DPB after multiple oral doses of DMMDPB in patients with essential tremor is shown in Figure 2.

Table 3 shows a comparison of the mean change in tremor score from baseline (Day -1) to a composite endpoint (average of Days 12 and 14) between those patients treated with the drug (DMMDBP) and those treated with a placebo. The mean absolute change in the treated group was 18.3 as compared to 8.0 in the placebo group. This difference is statistically significant using a 2-tailed Student's t-test for independent groups ($p=0.05$).

TABLE 3

Treatment	N	Baseline Tremor Score (Day -1)	Absolute Change From Baseline Tremor Score (Day -1)	P Value ¹
Placebo	3	25.0	-8.0	0.05
Drug	8	32.0	-18.3	

N is the number of patients in the group.

¹ Patient's t-test, treated vs. placebo, 2-tailed

Table 4 shows a comparison of the linear trends in tremor score from baseline (Day 0) to a single endpoint (Day 14) between the group of patients treated with the drug (DMMDBP) and the group of patients given a placebo. All the data points between Day 0 and Day 14 were used in this analysis. The respective baseline and Day 14 performance scores were 32.0 and 13.9 in the treated group as compared to 25.0 and 16.0 in the placebo group. The treated and placebo performance score linear trends from Day 0 to Day 14 were found to differ significantly using a 2-factor mixed ANOVA model followed by a 1-tailed F-test for comparison of linear trends (p=0.05). In using this repeated measures statistical approach, the linear trends were observed within subject, with between subject effects being filtered out.

TABLE 4

Treatment	N	Baseline Tremor Score (Day -1)	Absolute Change From Baseline Tremor Score (Day -1)	P Value ¹
Placebo	3	25.0	16.0	0.05
Drug	8	32.0	13.9	

N is the number of patients in that treatment group.

¹ Difference in linear trend, treated vs. placebo, 1-tailed.

Example 3 – Treatment of Parkinson's Disease

Patients with treated, symptomatic Parkinson's disease are often troubled by tremor, by dystonia and chorea movements (dyskinesias) secondary to dopaminergic agents and by prominent motor fluctuations throughout the day ("wearing-off" or "on-off"). In addition, Parkinson's disease may sometimes have some intrinsic dystonic features. All of these tremor features may potentially be alleviated by treatment with T2000 or related compounds.

We will select 25 patients having on-off phenomena and 25 patients with tremor (the two groups may partially overlap, i.e., some patients may exhibit both syndromes). These patients will be treated with from 400 up to 800 mg of DMMDPB orally each day for two to three weeks. Patients will be monitored every other day to evaluate the degree of reduction in tremor and time in the “off” state as indicated using a modification of the Unified Parkinson’s Disease Rating Scale (UPDRS). Koller, W.C., and Tolosa, E., Current and Emerging Drug Therapies in the Management of Parkinson’s Disease, 50(6): S1-S48 (1998). It is anticipated that after two weeks of treatment, the treated patients will show a 25-50% reduction in tremor and a greater than about 10% in the time-off state as evidenced by routine neurologic examination.

Improvement in dyskinesia (dystonia and chorea) will also be assessed. Preliminary observations indicate that dystonic symptoms (e.g., writer's cramp) in patients with essential tremor are alleviated by therapy using 450 mg per day of DMMDPB to treat tremor. It is thus anticipated that the aforementioned regime will show effectiveness in dystonia and more generally dyskinesia of patients with Parkinson's disease.

Example 4 – Treatment of essential tremor with a Phosphonooxymethyl Derivative

Twenty patients will be selected using criteria for definite essential tremor as classified by the National Institute of Health (NIH) Diagnostic Criteria for Essential Tremor and the Tremor Investigation Group (TRIG) Proposed Criteria for Diagnosing Essential Tremor. See Jankovic J. Essential Tremor: Clinical Characteristics, Neurology, 2000;54 (Suppl 4); S21-25, incorporated by reference in its entirety. According to these protocols, patients must have bilateral postural tremor of both upper extremities with an amplitude rating of 2 or greater in one arm and 1 or greater in the other, which is visible, persistent, and longstanding (preferably > 3 years). Patients will be tapered off medications and vitamins, energy drinks, grapefruit and supplements 7 days prior to the commencement of the study. They will be instructed to stop tremor medications 14 days prior to study commencement, after taper.

The patients will be randomized to receive phosphonooxymethyl derivatives, 400 mg twice daily in the morning and evening (12 hours apart, total daily dose 800 mg) or

placebo (9 patients on drugs, 3 on placebo) for 14 days. Patients will be confined one day prior to dosing and for the initial two days of dosing for the baseline neurological assessment. Evaluations of tremor will be conducted on days 0, 1, 2, 4, 6, 8, 10, 12, 14, 15, 16, 18, 20 and at least 2 weeks after termination of treatment using established rating methods. See Fahn S. *et al.*, Clinical rating scale for tremor, In: Parkinson's Disease and Movement Disorders, Jancovic J., Tolosa E. (Eds.) 1998 Urban & Swarzenberg, Inc. Baltimore, MD, USA 225-34. Concurrent plasma concentrations of phosphonooxymethyl derivatives, MMMDPB and DPB will be measured. Blood samples will be collected on days 1, 2, 4, 6, 8, 10, 12, 14 and during morning visits on days 16, 18, 20, 22 and at 2, 4, 8 and 12 hours past the trial administration.

Evaluations of tremor will be conducted with at least one of a clinical rating scale, a patient-reported disability/symptom scale, and neurophysiological measurements, such as accelerometric recordings. Since the correlation between accelerometry scores and functional disability scores has been subject to criticism in the literature, clinical grading scales and patient reporting will be used as the primary parameters. On unblinding, we expect that patients treated with phosphonooxymethyl derivatives will have shown a significantly decreased tremor as opposed to patients treated with placebo.

* * * * *

The embodiments illustrated and discussed in this specification are intended only to teach those skilled in the art the best way known to the inventors to make and use the invention. Nothing in this specification should be considered as limiting the scope of the present invention. Modifications and variation of the above-described embodiments of the invention are possible without departing from the invention, as appreciated by those skilled in the art in light of the above teachings. It is therefore understood that, within the scope of the claims and their equivalents, the invention may be practiced otherwise than as specifically described.

All patents, applications, publications, test methods, literature, and other materials cited herein are hereby incorporated by reference.